## REMARKS/ARGUMENTS

Upon entry of the present amendment, claims 103, 105-113, 118 and 120-140 are pending. Claims 104, 114-117 and 119 are canceled without disclaimer or prejudice to renewal. Claims 103, 105-109, 110, 112, 118, 120-123, 125, 127 and 138-140 are amended. Claim 103 is amended to incorporate the language of claim 104. Claim 118 is amended to incorporate the language of claim 119. Claims 105-109, 112, 120-123 and 127 are amended to properly depend from a pending claim. Claims 103, 110, 118, 125, 138-140 are amended to clarify that the peptide consists of the recited amino acid sequence. No new matter is added by the present amendments, and the Examiner is respectfully requested to enter them. No amendment should be construed as acquiescence in any ground of rejection. Lack of comment on any of the Examiner's remarks should not be construed as agreement therewith.

### *Claim Objections*

The Examiner objected to claim 103 because the claim did not define Aβ at its first mention. In response, Applicants have amended claim 103 to define Aβ.

The Examiner objected to claims 104-113 because claim 103 recites the "consisting of" closed language with respect to the amino acids sequence of KLVFFAED (residues 16-23 of SEQ ID NO:1). The closed language defines the Aβ fragment as being no longer than and consisting of only the amino acid residues of KLVFFAED, but does not preclude linking the fragment as defined to a carrier. Applicants respectfully submit that the inclusion of a carrier to an Aβ fragment defined by closed language, *i.e.*, to exclude additional residues of Aβ, does not improperly broaden the fragment. As set forth in amended claim 103, the Aβ fragment still consists of KLVFFAED (residues 16-23 of SEQ ID NO:1), and it is linked to a carrier. Accordingly, the Examiner is respectfully requested to withdraw this rejection.

***Rejection under 35 U.S.C. § 101***

Claims 103 and 114-117 are rejected under 35 U.S.C. § 101 as allegedly directed to non-statutory subject matter. Applicants do not agree with the Examiner's position. However, in the interest of furthering prosecution, Applicants have amended claim 103 to set forth that the fragment is linked to a carrier and canceled claims 114-117.

***Rejection under 35 U.S.C. § 112, second paragraph***

The Examiner has rejected claims 114-117 under 35 U.S.C. § 112, second paragraph, as allegedly indefinite. Applicants do not agree with the Examiner's position. However, in the interest of furthering prosecution, Applicants have canceled claims 114-117. Accordingly, the Examiner is respectfully requested to withdraw this rejection.

***Rejection under 35 U.S.C. § 102(b)***

The Examiner has rejected claims 103 and 114-117 under 35 U.S.C. § 102(b) as allegedly anticipated by WO 96/39834 ("Soto-Jara"). Applicants do not agree with the Examiner's position. However, in the interest of furthering prosecution, Applicants have amended claim 103 to set forth that the fragment is linked to a carrier and canceled claims 114-117. The Examiner acknowledges that Soto-Jara does not teach an Aβ fragment consisting of KLVFFAED (residues 16-23 of SEQ ID NO:1) linked to a carrier, and claim 104 was not included in this rejection. *See*, the present Office Action at page 8 bridging to page 9. Accordingly, the Examiner is respectfully requested to withdraw this rejection.

***Rejections under 35 U.S.C. § 103(a)***

Soto-Jara in view of Schenk

Claims 103-109, 112-124, 127, 132-135, 137 and 138 stand rejected under 35 U.S.C. § 103(a) as alleged rendered obvious over Soto-Jara in view of WO 99/27944 ("Schenk"). To the extent that the present rejection applies to the amended claims, Applicants respectfully traverse.

The Examiner alleges that Soto-Jara discloses a fragment of Aβ consisting of amino acid residues 16-23 and that Soto-Jara calls this peptide "amyloid β peptide." *See*, the present Office Action at page 6 bridging to page 7. The Examiner acknowledges that Soto-Jara does not teach the fragment of Aβ conjugated to a carrier or as part of a pharmaceutical composition. *See*, the present Office Action at page 8 bridging to page 9. However, the Examiner alleges that Schenk teaches methods of treatment of a disease characterized by amyloid deposition by inducing an immune response against a peptide component of an amyloid deposit by administering an Aβ peptide, *i.e.*, amyloid β-peptide. *See*, the present Office Action at page 9.

Soto-Jara reports that residues 16-23 of Aβ may have a role in adopting a β-sheet secondary structure contributing to amyloid deposits. *See*, Soto-Jara, *e.g.*, at page 4, lines 17-35; at page 9, lines 14-35; at SEQ ID NO:1 on page 35; and in Figure 1A. Soto-Jara proposes using several so-called anti-amyloid peptides (*i.e.*, SEQ ID NOs: 7-10 in Soto-Jara) in a regime where the anti-amyloid peptides directly bind to a hydrophobic structural determinant on an amyloid peptide to prevent aggregation. *See*, Soto-Jara, *e.g.*, at Figures 2A and 9, and at page 9, line 36 through page 10, line 5. This regime does not require an immune response. In fact, Soto-Jara teaches that various amino acid modifications such as an amide or pyroglutamyl residue be incorporated to reduce immune responses (Soto-Jara at page 15, line 38 to page 16, line 6).

If the proposed modification or combination of the prior art would change the principle of operation of the prior art invention being modified or render it unsuitable for its intended purpose, then the teachings of the references are not sufficient to render the claims *prima facie* obvious. MPEP § 2143.01(V-VI). Moreover, a reference teaching away from an invention is strong evidence of non-obviousness, in fact, the very antithesis of obviousness, to which a rebuttal should not even be required. *In re Buehler*, 185 USPQ 781 (CCPA 1975); *In re Hedges*, USPQ 685, 687 (Fed. Cir. 1986). Here, the proposed modification of Soto-Jara changes the principle of operation of Soto Jara, renders the peptide unsatisfactory for Soto-Jara's intended purpose and is contrary to Soto-Jara's teaching. As discussed above, Soto-Jara proposes a direct role of peptides in blocking aggregation, not a role of inducing antibodies. The Examiner's proposed modification to include a carrier to help elicit an immune response changes the

principle of operation by having the peptide act not directly, as contemplated by Soto Jara, but by a distinct mechanism in which the peptide induces antibodies, which in turn acts to reduce amyloid deposits. The Examiner's proposed modification also renders the peptides of Soto-Jara unsatisfactory for its intended purpose of direct inhibition of amyloid aggregation because promoting an antibody response against the peptide would clear it from the circulation faster reducing or eliminating their opportunity to inhibit amyloid aggregation. The carrier may also sterically interfere with the ability of Soto-Jara's peptides to effect direct inhibition of amyloid aggregation. Furthermore, the proposed modification is directly contrary to Soto-Jara's teaching to reduce, not increase, immunogenicity of peptides. Because modifying the compositions of Soto-Jara to make them more immunogenic changes the principle of operation of Soto-Jara, renders the peptides unsuitable for Soto-Jara's intended purpose and is directly contrary to the teaching of Soto-Jara, the modification was not obvious.

Furthermore, in alleging that it was predictable that immunizing with an Aβ fragment consisting of KLVFFAED linked to a carrier would produce an immune response useful for the treatment or prevention of a disease characterized by amyloid plaques, *e.g.*, Alzheimer's disease, the Examiner omits to mention that whereas immunization with an Aβ1-5 conjugate achieved a statistically significant reduction in levels of Aβ in the brain, active immunization with an Aβ13-28 conjugate did not. *See, e.g.*, Figure 12 of Schenk. Efficacy of the claimed conjugate, which includes a subfragment of Aβ13-28 is shown in the attached declaration of Dr. J. Steven Jacobsen. The declaration reports improvement in cognitive properties from immunizing an art-recognized model of Alzheimer's disease with an Aβ16-23 conjugate. Given the results reported for the Aβ13-28, the efficacy reported by Dr. Jacobsen of the claimed conjugate, which represents a subfragment of Aβ13-28, was not predictable from the cited art.

For the foregoing reasons, withdrawal of the rejection is respectfully requested.

Soto-Jara in view of Schenk further in view of WO 00/72876

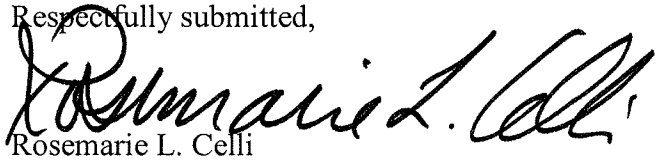
Claims 110, 111, 125 and 126 stand rejected as allegedly obvious over Soto-Jara in view of Schenk in further view of WO 00/72876. The Examiner cites WO 00/72876 for disclosing additional carriers. This rejection is respectfully traversed for at least the same reasons as for the other claims.

Soto-Jara in view of Schenk further in view of WO 01/78777

Claim 136 stands rejected as allegedly obvious over Soto-Jara in view of Schenk in further view of WO 01/78777. The Examiner cites WO 01/78777 for disclosing RC-529. This rejection is respectfully traversed for at least the same reasons as for the other claims.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 650-326-2400.

Respectfully submitted,



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